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Early onset pneumonia: a multicenter study in intensive care units

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Abstract. A prospective multicenter study concerning the incidence, onset time, risk factors and mortality of pneumonia was carried out by the Intensive Care Units Collaborative Group for Infection Control in Lombardy, Northern Italy. Out of 1304 patients admitted over 3 months in 16 intensive care units (ICUs), 441 met the criteria for the protocol (no previous pulmonary infection or irreversible terminal illness, ICU stay > 48 h). The incidence of acquired pneumonia was 21.3% (94/441), with 54.2% of cases diagnosed within 4 days of admission (early onset pneumonia). Impairment of airway reflexes on admission and more than 24 h respiratory assistance were shown as significant risk ractors (RR) for early onset pneumonia (respectively RR = 12.4, with 95% confidence interval (CI) = 5.3–28.9 and RR = 3.3, with 95% CI = 1.8–5.9). A suggested pathogenetic mechanism is aspiration of oropharyngeal contents at the onset of acute illness, due to depression of protective reflexes with delayed clearance of bacterial contamination. No protection was offered by routinely applied prophylactic antibiotic therapy.

Key words: Pneumonia – intensive care unit – Epidemiology – Risk factors

Infection is frequently the limiting factor for the success of treatment in intensive care units (ICU). The most specific infectious complications in ICU patients are pneumonia and bacteremia [11, 25]. Bacteremia has been extensively studied and its physiopathological and epidemiological aspects reviewed [17] and some guidelines for successful prevention and research directions are generally accepted. Pneumonia in ICU is more complex: reported incidences range from 1.5 to 21.6% [8, 9, 22], microbiological and clinical diagnosis may be very difficult and controversial [23] and the mortality rate of patients with lung infection is considerable [15, 22]. Moreover, the lung is the main original site of infection in patients who die of adult respiratory distress syndrome (ARDS) and multiple organ failure [2].

Greater attention to respiratory equipment has been reported as a successful approach in epidemic pneumonia [21]. However, two longitudinal studies [7, 15] report unchanged pneumonia rates despite careful attention to decontamination and sterilization protocols and teaching of ICU personnel. An adequate standard of hygiene thus represents a prerequisite to prevent epidemics of pneumonia, but seems insufficient to prevent lower respiratory tract infection in the non-epidemic context.

In a previous study [16], oriented more to patient – than device – related risk factors, we found a surprisingly high incidence of pulmonary infections diagnosed within the first days of admission, unlikely related to equipment contamination [4–6], acquired immunodeficiency or irreversible underlying disease. The present study was therefore planned to describe ICU pneumonia more extensively, aiming to differentiate pneumonia according to its onset, to verify its incidence and characteristics in a representative multicenter study. Some typical clinical conditions, such as impaired airway reflexes at admission and need for

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prolonged respiratory assistance, were investigated as possible risk factors. The study should also provide information about the routine prophylaxis in our area and its role in pneumonia prevention.

Materials and methods

Patients admitted during a 3-month period (April–June 1983) to 16 (15 general and 1 neurosurgical) ICUs, representing 50% of intensive care resources of the Lombardy region for a catchment area of 4.5 million people, were considered for the study. Data were prospectively collected by ICU physicians in ad hoc pretested forms. Because of the descriptive nature of the study protocol, no specific changes to the general care and antimicrobial policy in use were requested.

The inclusion criteria were: absence of pulmonary infection on admission to ICU, absence of rapidly irreversible pathology and ICU stay > 48 h. Excluded, therefore, were patients admitted only for a brief period of surveillance or who died within the first phase in which infections are not relevant for survival.

Patients were grouped according to their main diagnosis in categories: *trauma:* trauma patients even if surgery was performed; *postsurgical status:* patients after major elective or emergency surgery or because of severe postoperative complications; *cardiopathy:* mainly patients with complicated myocardial infarction; *intoxication:* exogenous intoxications (mainly self-poisonings); *neuromuscular disorders:* patients with myasthenia gravis or polyradiculoneuritis; *miscellanea:* heterogeneous group. Diagnosis of pneumonia was accepted if consistent clinical criteria, purulent discharges and new and persistent X-ray infiltrations were present [3]. Full microbiological data were not required for diagnosis; available routine culture results from tracheobronchial or blood specimens were taken into account if relevant and consistent, in agreement with Bartlett [1]. For the purpose of this study, cases were considered as early onset pneumonia (EOP) if diagnosis was made within four days of admission. Airway reflexes were considered impaired (IAR) when spontaneous breathing, glottic closure and cough reflexes were impaired or absent at admission, and there was no defence reaction to endotracheal intubation or pharyngeal suctioning. No attempts were made to quantifty IAR and only "impaired" or "not impaired" was reported in the form.

Respiratory assistance for more than 24 h (RA > 24 h) was chosen as a limit to distinguish short-lasting and prolonged ventilatory support delivered in any form through an endotracheal tube.

Early antibiotic treatment (prophylaxis) was administered according to the decision of the house staff and computed as present or absent.

Statistical analysis was done by the chi-square test and the relative risks (RR) were calculated with their 95% approximate confidence interval (CI) for EOP in relation either to IAR on admission or to the presence of IAR with variable length of respiratory assistance (RA) or to the prophylactic antimicrobial regimen adopted by the hospital [10].

The effects of IAR, RA > 24 h and prophylaxis were considered separately within the various strata of potential confounding factors by the Mantel-Haenszel procedures [18, 19].

Results

Out of the 1304 hospital patients 441 met the inclusion criteria; their predominant pathologies were: trauma, 147 patients; postsurgical status, 96; cardiopathy, 53; intoxications, 37; neuromuscular disorders, 11; miscellanea, 97. Among the variables studied as risk factors for pneumonia, IAR was present in 53.7% (234/436 with 5 missing cases); in 33.3% of the samples (144/432 with 9 missing cases) respiratory assistance was necessary for longer than 24 h. All ventilated patients except one had IAR.

All pneumonia and EOP cases, in all cases and in "at risk" patients, are reported in Table 1. No patient had more than one pneumonia episode.

Overall pneumonia incidence in our samples was 21.3% (94/441 cases); EOP accounted for 54.2% (51/94) corresponding to 11.6% of the total study population (Fig. 1). EOP was diagnosed in 20.1% (47/234) of the IAR population and in 20.8% (30/144) of the patients with IAR and RA > 24 h. The importance of IAR with respect to the occurrence of EOP is even clearer from its very low overall incidence in not IAR patients (2%; 4/202), whereas 92% of EOP had IAR.

The estimated crude relative risk of EOP for 234 patients with IAR was 12.4 (with 95% CI = 5.3–28.9) (Table 2). The risk was broadly consistent within various strata of age, sex, origin of patients (in or out of hospital), the variability of the risk estimates being well within the limits of random variation. In IAR patients RA > 24 h did not result in a significant risk for EOP (RR = 1.07, with 95% CI = 0.55–2.10) and the risk of EOP in IAR + RA > 24 h patients was the same as for IAR patients not needing prolonged ventilation (RR = 12.2 vs RR = 12.4). Allowance for all potential confounding factors by the Mantel-Haenszel procedures did not appreciably change the overall risk. Age, sex, tracheal intubation and patient origin (in or out of hospital) did not represent by themselves a risk for pneumonia.

The underlying pathology as a confounding factor could not be analysed because of the lack of a single

Table 1. General picture of all and at-risk patients in relation to pneumonia event

	Patients	Pneumonia		Early onset pneumonia		
	(no.)	(no.)	(%)	(no.)	(%)[a]	(%)[b]
All patients	441	94	21.3	51	11.6	54.2
– with IAR	234	78	33.3	47	20.1	60.2
– with RA>24 h	144	55	38.2	30	20.8	54.5
– with IAR+RA>24 h	143	55	38.4	30	20.9	54.5
– with IAR not RA>24 h	86	23	26.7	17	19.7	73.9
– not IAR not RA>24 h	202	16	7.9	4	1.9	25.0
Prophylaxis cases	251	55	21.9	27	10.7	49.1
– with IAR	132	40	30.3	23	17.4	57.5
– with RA>24 h	79	30	38.0	15	19.0	50.0

[a] % of all patients; [b] % of pneumonia cases. IAR = impaired airway reflexes; RA>24 h = respiratory assistance for more than 24 h

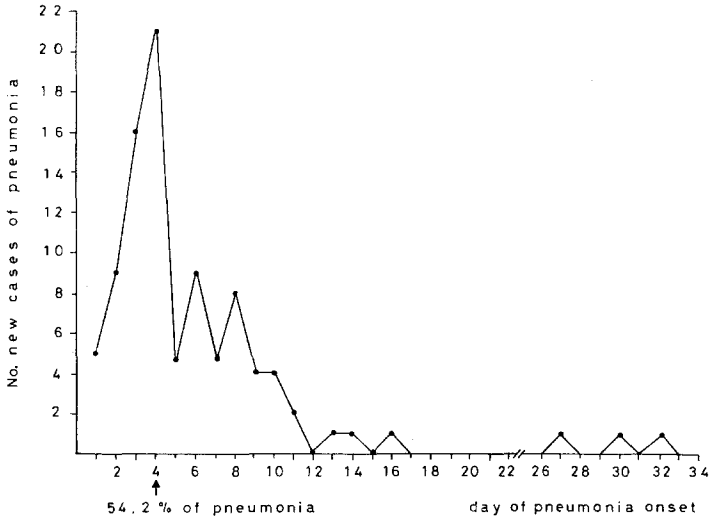

Fig. 1. Frequency of pneumonia cases in relation to the time elapsed from ICU admission

subset. Figure 2 shows, however, the correlation between the different incidence of IAR in the various groups and the incidence of EOP.

Antibiotic prophylaxis was given to 56.9% of the patients (251/441) with an interhospital range of 17.2–100%. Penicillins (penicillin G, ampicillin or piperacillin), cephalosporins and aminoglycosides were the most extensively used drugs (respectively 45.7%, 24.6% and 12% of total prescriptions). When expressed in term of RR, prophylaxis did not seem to ensure any protection against EOP in the overall population (RR = 0.83, with 95% CI = 0.5–1.5) or in high risk patients, i.e. IAR+RA>24 h (RR = 0.78, with 95% CI = 0.3–1.7). The risk estimates for prophylaxis were not modified when considered within strata of various covariates.

Microbiological tests were positive in 54.9%, not performed in 27.5% and negative in 17.6% of EOP cases; Gram-negative bacteria accounted for 46.4%, Gram-positive for 39.3%, mixed infections for 14.2% of microbiologically documented EOPs. The isolated strains for in- and out-patients are listed in Table 3.

Table 2. Relative risk of early onset pneumonia according to airway reflexes impairment (IAR) or/and protracted respiratory assistance (RA>24 h) in overall and selected population

At-risk group/control	group	RR	95% CI
Patients with IAR/Patients without IAR		12.40	5.35–28.90 (S)
Patients with RA>24 h/Patients without RA>24 h		3.30	1.88–5.95 (S)
Patients with IAR, without RA>24 h/Patients without IAR, without RA>24 h		12.20	4.83–3.07 (S)
Patients with IAR and with RA>24 h/Patients with IAR, without RA>24 h		1.07	0.55–2.10 (NS)

IAR = impaired airway reflexes; RA>24 h = respiratory assistance for more than 24 h; S = significant; NS = not significant

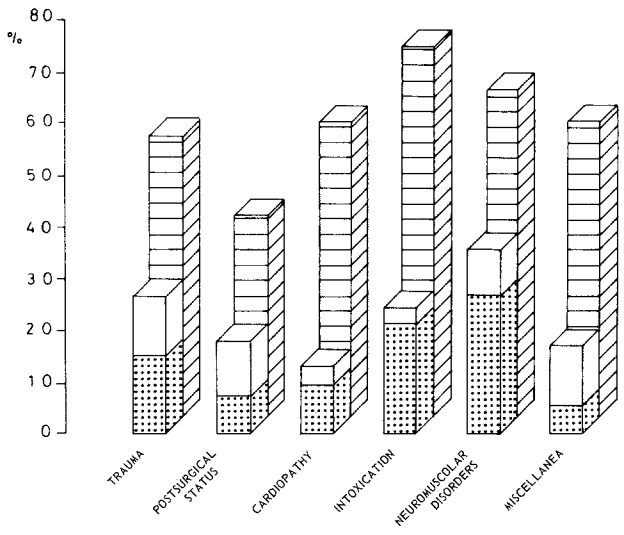

Fig. 2. Correlation between EOP and IAR in diagnostic categories. 1st column: incidence of pneumonia, stippled area representing EOP. 2nd column: incidence of IAR patients

Table 3. Classification of strains isolated from microbiologically documented early onset pneumonia in in- and outpatients

	Total cases	Cases with					
		Gram-negative rods		Gram-positive rods		Mixed flora	
	(no.)	(no.)	(%)	(no.)	(%)	(no.)	(%)
In-patients	11	7	63.6	3	27.3	1	9.1
Out-patients	17	6	35.3	8	47.0	3	17.6
All patients	28	13	46.6	11	39.3	4	14.2

Overall mortality was 19.9% (88/441). Among pneumonia cases 31.4% (16/51) of EOP and 46.5% (20/43) of patients with late onset pneumonia died. A causal relation between a specific clinical entity and mortality is always difficult in ICU, because of the major pathology correlation factors, we can only state that the mortality rate in patients who contracted pneumonia during the hospital stay (36/94) was double that of patients without pneumonia (52/347).

Discussion

The overall incidence and the concomitant rise in mortality document that pneumonia is a frequent critical event in an ICU setting. While only seldom reported as a separate category in the literature [12, 16], EOP seems to be a well defined disease entity, whose quantitative importance (54% of all pneumonia cases) imposes a better understanding of pulmonary involvement in ICU and of the relationship between clinical and setting-dependent risk factors.

The profile of EOP that emerges from the various pieces of information can be described as follows: EOP may appear, independently of age and sex, even in healthy subjects before the acute illness and without any evidence of immunological failure. The association of the highest risk estimate (IAR at admission) together with the microbiological data, indicating only rarely typical nosocomial bacteria in patients not previously hospitalized, suggests aspiration of oropharyngeal content at the acute onset of a severe event inducing impairment of airway reflexes – via depressed consciousness, chest pain, shock or therapeutic interventions – as an obvious pathogenetic candidate. The strength of the association of RA > 24 h with EOP goes in the same direction as previous studies about the association of respiratory assistance and acquired pneumonia [6, 11, 20], but also suggests a concomitant role secondary to IAR which could be more severe and longer lasting in patients who, together with impaired lung defence mechanisms, also show a protracted lack of spontaneous breathing activity. The incidental character of EOP, depending more on the acuteness of the onset than on the severity or reversibility of the lesion, might help to explain the better prognosis in term of mortality of EOP patients compared to patients with late onset pneumonia.

The different pathogenesis of later onset pneumonia probably includes modifications of the epithelial cells [13] and of the resident flora in the oropharynx [14]: generally gram-negative rods and fungi are recognized as dominant pathogens. These infectious complications often reflect a severe underlying illness and little is known about effective prevention: optimal care of respiratory equipment, asepsis in invasive maneuvres and adequate nutritional support seem important. Judicious use of antibiotics to change normal flora as little as possible and enhancing host defences against colonisation and pneumonia are recommended by La Force [15] and an interesting approach by selective decontamination of the oropharynx has been recently proposed [24].

If two distinct forms of pneumonia can be assumed to exist, EOP can be traced back to a causal event occurring in a very limited, well-defined period shortly before admission to the emergency room or ICU. A post-event and pre-infection approach with antibiotics seems reasonable, just as when protecting against infections after bone fractures or penetrating abdominal wounds.

The risk estimates in our study, however, suggest that antibiotic prophylaxis does not play an important role in the prevention of EOP. Because of the specific limitations intrinsic to an observational study and the widespread use of antibiotics in clinical practice, this aspect is now being tested in a large-scale multicenter

trial. Beside the specific question of the efficacy of antibiotic prophylaxis in preventing EOP, our experience stresses the need for a better knowledge of the "natural history" of pneumonia in the critically ill patient and restrains enthusiasm for device-oriented studies.

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